


## Comorbidity of metabolic syndrome components in a population-based screening program: A latent class analysis

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### Abstract

**Background:** The prevalence of metabolic syndrome (MS) is rapidly increasing in the world. Thus, the aim of the present study was to identify the latent subgroups of Iranian male adults based on MS components and investigate the effect of abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST), high total cholesterol (TC), and low-density lipoprotein (LDL) on the odds of membership in each class.

**Methods:** In the present study, we used the data of a population-based screening program conducted on 823 urban adult men aged 25 years and older in city of Qom in 2014. Abdominal obesity, fasting blood sugar (FBS), blood pressure, and serum lipid profile were measured in participants after for at least 8 hours. MS was defined according to the Adults Treatment Panel III criteria. Latent class analysis was used to achieve the aims of study. Analyses were conducted using PROC LCA in SAS 9.2 software. In all analysis,  $p$  value  $< 0.05$  was considered statistically significant.

**Results:** There were 3 different latent classes among participants. Latent class 1, non-MS, 55.1%; latent lass 2, at risk, 21.3%; and finally latent class 3, MS, with 23.6% of the participants. Age (OR=0.98, 95% CI: 0.98-0.99, high LDL (OR=0.27, 95% CI: 0.13-0.56), high TC (OR=8.12, 95% CI: 4.40-15.00), and abnormal ALT (OR=2.25, 95% CI 1.49-3.41) were associated with at risk class. Also, only age (OR=1.02, 95% CI: 1.01-1.04) was associated with MS class. The most prevalent components among the participants were having low HDL (34.0%) and high WC (33.9%).

**Conclusion:** Notable percent of samples fell in “at risk” and “MS” classes, which stress the necessity of designing preventive interventions for these specific stratum of population.

**Keywords:** Metabolic syndrome, Latent class analysis, Subgrouping, Iran

**Conflicts of Interest:** None declared

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### Introduction

The prevalence of metabolic syndrome (MS) which is also called syndrome X, insulin resistance syndrome, and

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#### ↑What is “already known” in this topic:

The prevalence of metabolic syndrome (MS) is rapidly increasing in the world. In Iran, its prevalence has been reported to be 23.8% to 36.9% in adults. Elevated ALT and AST may be risk factors for MS. There is limited information about the relationship of MS with NAFLD.

#### →What this article adds:

There were 3 different latent classes among participants of this study: Latent class 1, non-MS, 55.1%; latent lass 2, at risk, 21.3%; and latent class 3, MS, with 23.6% of the participants. This study showed that abnormal AST had no significant effect on the membership of adults in different classes. However, abnormal ALT increased the odds of membership in the second class (OR=2.25).

etc. is rapidly increasing worldwide (1, 2).

The cluster of metabolic factors for MS includes abdominal obesity, high blood pressure, low HDL, high triglyceride levels, impaired fasting glucose, and insulin resistance (3, 4). There is evidence that MS greatly increases the risk of developing type 2 diabetes, heart diseases, and mortality rates (2, 5). According to the International Diabetes Federation (IDF) reports, about 20%-25% of the world's adult population has MS. Individuals with MS have 2 times greater risk of mortality, 3 times greater risk of heart attack and stroke, and 5 times greater risk of diabetes (6).

Results of previous studies have shown high prevalence of MS in both Western and Asian countries (7-10). For example, the prevalence of MS was reported to be 32.3%, 33%, and 28.3% in England, India, and Saudi Arabia, respectively (9-11).

MS is a common condition in Iran and is associated with ethnicity, socioeconomic status, and diet. This syndrome can be diagnosed early in adolescence through measuring simple anthropometric indices (12). A number of studies conducted in Iran showed various prevalence of MS among adults ranging from 23.8% to 36.9%, which is relatively higher than the prevalence of MS among American adults (3, 13, 14). In a recent study, the overall prevalence of MS was estimated 23.0%, which was the highest in those 55 to 64 years (38.6%) (15).

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are markers of nonalcoholic fatty liver disease (NAFLD) (16). NAFLD is a component of MS; thus, elevated ALT and AST may be risk factors for MS (17). There is limited information about the relationship of MS with NAFLD.

The clinical definition of MS includes presence of 3 or more of its components. However, it does not matter that a person engages in which of the 3 components (18, 19). Understanding which MS components cooccur with each other is possible with subgrouping individuals based on these components (20). Identifying quantitatively and qualitatively different subgroups of MS components is possible with latent class analysis (LCA) (21). Considering distinct profiles of MS can help physicians, health policymakers, and health service providers in applying true decisions in prevention programs (19, 20).

The latent class analysis (LCA) is a structural equation model that divides individuals into distinct subgroups with respect to obvious variables. Since the probability of relationships between the components of MS is different in each subgroup, LCA may be useful in describing and identifying the characteristics of these individuals based on the components of MS. In Iran, a few number of studies applied this model to identify the pattern of MS and its components (20). However, this method was never used in previous population-based studies among Iranian adults. Moreover, the effect of abnormal ALT and AST, high total cholesterol (TC), and high LDL on MS components was not evaluated in previous studies. Therefore, the present study aimed to evaluate the pattern of MS by identifying latent classes of MS among Iranian adults and investigate the effect of abnormal ALT and AST, high TC, and high LDL on the odds of membership in each class.

## Methods

### Participants

In the present study, we used the data of a population-based screening program that was conducted among 823 urban adult men aged 25 years and older in city of Qom in 2014. In this study, participants were selected using multi-stage random sampling. First, the proportion of each district was calculated to select participants. Next, systematic random sampling was used to recruit participants in each stratum. Participants were men aged at least 24 years who were living in Qom, Iran. More details are described in our recent published articles (15, 22).

### Measurements

Data collection was designed in 2 stages. At the first stage, a self-report health interview survey was administered to evaluate participants' self-report health status and to collect demographic information. In the second stage, based on the study protocol, all participants were invited to take part in screening. A serum lipid profile was ordered for all participants after no caloric intake for at least 8 hours and the laboratory results were assessed. This profile included total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglyceride (TG), and hemoglobin tests.

In the present study, MS was defined based on the ATP III (23) criteria. According to this criteria, the presence of 3 or more of the following items considered as MS: (1) high blood pressure ( $\geq 130/85$  mmHg or a history of hypertension), (2) abdominal obesity (waist circumference  $> 102$  cm), (3) FBG  $\geq 110$  mg/dL (or a history of diabetes mellitus), (4) fasting HDL cholesterol  $< 40$  mg/dL, and (5) fasting TG  $\geq 150$  mg/dL. The more details of measurements were described in our recent articles (15, 22).

### Ethical consideration

All participants in the present study provided written informed consent, and ethical committee of Qom University of Medical sciences approved the study protocol.

### Statistical analysis

In this study, LCA was used for data analysis, which is appropriate for classifying the study participants into different categorical latent variables based on their homogeneity. This analysis assumes that the possible correlation of the indicator variables can be justified by latent variables categories by considering the measurement error. LCA determines the best model with different iterations for the number of identified latent classes and comparing the frequencies of the observed and expected response patterns. For each model, the LCA calculates G2 statistic. Also, Akaike information criterion (AIC) and Bayesian information criterion (BIC) were calculated based on G2 to select the final model (24). For these indices, a smaller value shows a more optimal balance of model fit and parsimony. Finally, a model with the minimum value of AIC or BIC may be selected.

**Table 1.** Comparison of different LCA models based on model selection criteria

Number of latent class	Number of parameters estimated	G <sup>2</sup>	df	AIC	BIC	P Value	Maximum log-likelihood
1	5	313.01	26	323.01	346.57	< 0.00001	-2407.55
2	11	77.49	20	99.49	151.33	< 0.00001	-2289.79
3	17	20.54	14	54.54	134.66	0.114015	-2261.32
4	23	8.48	8	54.48	162.88	0.388039	-2255.29
5	29	4.33	2	62.33	199.00	0.11475	-2253.21

Note: LCA=Latent class analysis, AIC=Akaike information criterion, BIC=Bayesian information criterion.

Five binary indicator variables were selected to perform LCA, and 5 dichotomous observable variables (eg, indicators) were used to subgroup the participants based on MS components as a latent variable. These indicators were high blood pressure (BP), abdominal obesity, fasting blood sugar (FBS), high-density lipoprotein (HDL), cholesterol, and triglyceride (TG). After finalizing the model, abnormal AST and ALT, high TC, high LDL, and age were entered as covariates in the model.

Given the 5 binary variables, a total of 32 response patterns were identified. Different measures of model assessment are presented in Table 1. Since the degree of freedom of G<sup>2</sup> statistic was less than 60 (G<sup>2</sup> was distributed approximately as chi-square), the overall significance of the estimated model (Goodness-of-fit) was computed using G<sup>2</sup> statistic. When this index is significant, it indicates a significant difference between expected and observed frequencies and, subsequently, it indicates that the fitted model is not appropriate.

The probability of a “No” response can be calculated by subtracting the item-response probabilities from 1. These probabilities form the basis for interpretation and labeling of latent classes. The larger conditional probabilities appear in bold font to highlight the overall pattern. Due to restrictions of doing complex latent class analysis in SAS software, all analysis was done without considering sampling weights. All analyses were done using PROC LCA in SAS 9.2 software (SAS Institute Inc. Cary, NC, USA). In all analysis, P value < 0.05 was considered statistically significant.

## Results

This study was conducted among 823 participants. Findings showed that the mean age of the participants was 54.30±18.81 years. Also, 214 (26.0%) of the participants were single. The prevalence of metabolic syndrome components is demonstrated in Table 2. Accordingly, low HDL (34.0%) and high WC (33.9%) were the most prevalent components in the participants.

Based on the results of Table 1, hence, 3, 4 and 5 class models were not significant. In the next stage, the best-fitted model was selected based on G<sup>2</sup>, AIC, and BIC. The model with the lowest G<sup>2</sup>, AIC, and BIC values is suitable. According to these model selection indices and interpretability of the results of the model, we concluded that the 3 latent class model was appropriate.

The results of the 3-class model showed that the difference of expected and observed frequency of response pattern was not statistically significant (G<sup>2</sup>=20.54, df=14, p=0.114). After selecting the final model, we entered age, total cholesterol, LDL, abnormal AST and ALT as covariates in LCA model.

Table 3 shows the results of LCA for the 3-class model. This table has 2 parts: latent class prevalence and item-response probabilities. Latent class prevalence or the probability of the membership in each latent class is presented in the first section of Table 3.

There are 3 different latent classes among participants. Latent class 1, non-MS, with 55.1% of the participants; latent lass 2, at risk, with 21.3% of the participants; and finally latent class 3, MS, with 23.6% of participants (Table 3).

**Table 2.** Percentages of metabolic syndrome (MS) components among Iranian male adults

Items	Total (n=823)		
	N	%	95% CI
High BP	227	27.6	25.5-30.6
High abdominal obesity	279	33.9	30.7-37.1
High FBS	166	20.2	17.6-23.1
Low HDL	280	34.0	31.0-37.6
High TG	204	24.8	22.0-28.0

**Table 3.** The 4 Latent classes model of components of metabolic syndrome

	Latent class		
	Non-MS	At risk	MS
Latent class prevalence	0.551	0.213	0.236
Item-response probabilities			
High BP	0.133	0.027	0.833
High WC	0.139	0.284	0.856
High FBS	0.092	0.135	0.522
Low HDL	0.275	0.586	0.284
High TG	0.005	0.805	0.319

Note: the probability of don't engaging in each components can be calculated by subtracting the item response probabilities shown above from 1.

\* item response probabilities >0.5 in bold to facilitate interpretation.

Table 4. Predictors of membership in latent classes of MS components pattern

Predictors	P value	C1	C2	C3
		OR (95%CI)	OR (95%CI)	OR (95%CI)
Age (year)	<0.001	Reference	0.98 (0.96-0.99)	1.02 (1.01-1.04)
High LDL	0.004	Reference	0.27 (0.13-0.56)	0.67 (0.33-1.37)
High TC	<0.001	Reference	8.12 (4.40-15.00)	1.76 (0.88-3.54)
Abnormal AST	0.629	Reference	0.87 (0.54-1.40)	1.24 (0.79-2.04)
Abnormal ALT	0.002	Reference	2.25 (1.49-3.41)	1.29 (0.84-1.96)

The conditional probabilities of positive response to having MS components are demonstrated in the second section of Table 3. The first class, named “non-MS,” included 55.1% of the study participants and was characterized by individuals exhibiting low probability for having all MS components. The second class, at risk, included 21.3% of the participants and was characterized by persons who had high probability for having low HDL and high TG. The third class, MS, included 23.6% of the participants and was characterized by individuals exhibiting high probability of having high BP, WC, and FBS.

The first row of Table 3 shows the probabilities of membership in each latent class. For example, latent class 1, Non-MS, included almost 55% of the participants and latent class 3, MS, included 23.6% of the participants.

Table 4 shows the odds ratios of membership in each latent class. For simplicity of interpretation, the first class (non-MS) was considered as a reference class, and membership in latent classes 2 and 3 was calculated compared to latent class 1. This table indicates that having high LDL decreases the odds of membership in class 2 compared to class 1. Also, having high TC increases the odds of membership in class 2 compared to class 1. This table shows that having abnormal AST have no significant effect on membership of participants in different classes compared to the first class.

## Discussion

In this study, we identified latent subgroups of adults based on metabolic syndrome components using LCA and we were able to detect 3 separate classes: non-MS, at risk, and MS. The probability of engaging in each component of metabolic syndrome was low in the first class (non-MS). In the second class (at risk), however, the probability of having high HDL and high TG was high. In latent class 3 (MS), the probability of having high blood pressure, high abdominal obesity, and high FBS was high. There are 2 main groups of analysis in quantitative research: variable-centered and person-centered. Variable-centered analysis includes correlations, ANOVAs, path models, and regressions, which only assess the relationship between variables. Person-centered analysis includes cluster analysis and latent class analysis, which are used to investigate how variables are combined across individuals. Unlike variable-centered analysis that determines how characteristics are related to each other, person-centered analysis investigates how these variables group within individuals. As a result, LCA (as a person-centered analysis) can facilitate targeting future intervention resources to subgroup of adults based on MS components that promise to show the maximum treatment response (25, 26).

In this study, only 1 latent class (the third class) had high

probability for at least 3 components of MS consistently. In other words, the prevalence of metabolic syndrome was estimated as nearly 24% with LCA. On the other hand, about 21% of the participants were at risk for developing metabolic syndrome (the second class). The third class (MS) may indicate a clinical pathway generating the observed features of metabolic syndrome. From prevention view, the policymakers should focus on blood pressure, abdominal obesity, and fast blood sugar for reducing the probability of engaging in cardiovascular diseases, type 2 diabetes, and other complications of metabolic syndrome. In the second class, low HDL and high TG cooccurred among 21% of the participants. Understanding how the metabolic syndrome components comorbid and cluster together in the latent classes 2 and 3 can help clinicians to interpret the pathophysiology of metabolic syndrome. A similar study among Iranian adults showed that abdominal obesity had an important role in classifying the study samples (20). In the present study, we found that some variables have high probability only in 1 class. It seems that for prevention programs, all these variables should have same importance. Nonetheless, results indicated that interventions for reducing the prevalence of blood pressure, abdominal obesity, and fasting blood sugar should be in priority, because of the high prevalence of latent class 3 compared to class 2. The most important finding in LCA model was that among persons in latent class 3, some components of metabolic syndrome (low HDL and high TG) did not play an influential role in classifying the participants. On the other hand, these factors have high probability in the second class. In other words, about 45% of the study sample engaged with 2 or 3 components of MS. The participants of this study had different patterns of MS components. Nevertheless, based on the results of this study, it seems that integrated interventional programs should be designed to reduce the prevalence of all components of MS.

Only a few published studies used LCA to identify the latent classes of metabolic syndrome components. In addition, the researchers have used different criteria to specify subgroups. Also, the study samples were different among similar studies.

Edward et al found 3 latent classes of metabolic syndromes among nondiabetic individuals. They showed that only 1 latent class was strongly associated with all MS components. Moreover, they found another latent class that was associated with hyperglycemia and hypertension (19).

Another study indicated that among participants of the multiethnic study of atherosclerosis (MESA) participants, there were 3 latent classes of MS components. The authors named them as non-MS, low risk, and MS. They found that 29.9% and 35.4% of females and males were in latent class, respectively (18).



Abbasi-Ghahramanloo et al identified 4 latent classes of MS in Iranian adults: (1) non-MS (38.4%), (2) low-risk (18.6%), (3) high-risk (24.2%), and (4) MS (18.7%). In other words, in this study, about 19% of the participants had a low-risk and 24% a high-risk of developing MS (20). In comparison to Abbasi-Ghahramanloo et al study, our findings indicated that 21.3% of the participants were at risk of MS and 23.6% were engaged with MS. The best reason for this difference could be related to gender of the participants. Our study focused on men only.

Prior studies stated that triglyceride (TG) is an independent risk factor in developing CVD (27). On the other hand, it proposed that increased TG production in the liver due to insulin resistance preferentially produces TG-rich very low-density lipoprotein = s (VLDL), which finally generates small dense-LDL particles (28). The association of TG concentration and LDL has been shown in a variable-centered study (29). In the present person-centered study, the results showed that having high TG increases the odds of membership in the second class and having high LDL significantly reduces the odds of membership in the second class (OR = 0.27, 95% CI = 0.13-0.56). In the second class, the probability of having low HDL is high too and the effect of high LDL is not related only to high TG.

The present study indicated that having abnormal ALT increases the odds of membership in latent class 2 (OR = 2.25, 95% CI = 1.49-3.41). ALT as a marker of liver injury have been associated with dyslipidemia, including triacylglycerols and low HDL (30-33). Our study also showed that abnormal ALT had no significant effect on the third latent class. Previous findings indicated that the ALT level is associated with gender of the participants and body mass index in the general population (34). These 2 factors were not assessed in our study.

In this study, we identified latent classes of MS among a sample of men who were living in Qom for the first time. However, as a limitation, it was not clear how many people were unaware of their status or were not treated. Also, we were unable to subgroup and compare clustering of the participants in different demographic groups such as smokers versus nonsmokers and other relevant factors.

## Conclusion

Our study showed the separated subgroups of MS components among a sample of Iranian men. Results indicated that notable percent of samples fell in "at risk" and "MS" classes, which stress the necessity of designing preventive interventions with considering risk factors for these specific stratum of population.

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## Conflict of Interests

The authors declare that they have no competing interests.

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